ELSEVIER

Chronic Antidepressant Treatment Down-Regulates the Induction of c-fos mRNA in Response to Acute Stress in Rat Frontal Cortex

Shigeru Morinobu, M.D., Masashi Nibuya, M.D., and Ronald S. Duman, Ph.D.

The present study examines the influence of electroconvulsive seizure (ECS), as well as several antidepressant drug treatments, on the induction of c-fos mRNA in response to acute restraint stress. Acute (45-minute) restraint stress resulted in five- to sixfold elevation of c-fos mRNA levels in rat frontal cortex. Chronic administration of ECS significantly decreased the induction of c-fos mRNA levels in response to acute restraint stress, and this effect was observed after chronic (6 to 9 days) but not acute (1 or 3 days) of ECS treatment. In addition, c-fos induction in response to acute restraint stress was down-regulated by chronic, but not acute, administration of tranylcypromine or imipramine, two drugs that nonselectively increase synaptic levels of norepinephrine and serotonin by inhibition of monoamine oxidase or neurotransmitter reuptake, respectively. Moreover, chronic administration of desipramine or sertraline, selective re-uptake inhibitors of norepinephrine, or serotonin, respectively, also significantly down-regulated the induction of c-fos mRNA in response to restraint stress. Chronic administration of ECS, tranylcypromine, or imipramine also decreased stressed-induced levels of NGFI-A mRNA, another immediate early gene transcription factor, whereas levels of c-jun mRNA were not influenced by either stress or antidepressant treatments. The results demonstrate that chronic, but not acute, administration of ECS and several different classes of antidepressant drugs down-regulates stress-induced levels of c-fos mRNA, suggesting that this effect may be a common, postreceptor action of antidepressant treatments.
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KEY WORDS: *Electroconvulsive seizure; Tranylcypromine; Imipramine; Desipramine; Sertraline; c-fos*

Immediate early gene (IEG) transcription factors, such as c-fos, are induced in response to a variety of extracellular stimuli (Curran 1988; Morgan and Curran 1991). This rapid expression of c-fos has been utilized as a marker of increased metabolic activity and/or increased neuronal activity in brain (Sagar et al. 1988). Moreover, expression of c-fos and other IEG transcription factors is thought to represent an early stage in a cascade of intracellular events leading to regulation of other neuronal target proteins, and thereby could mediate more long-term adaptations of neuronal function (Curran 1988; Morgan and Curran 1991).

Electrically or chemically induced seizures have been shown to generate robust and rapid elevation of c-fos expression in brain (Dragunow and Robertson 1987; Morgan et al. 1987; Sagar et al. 1988; Winston et al. 1990). In a previous study, we reported that chronic administration of electroconvulsive seizure (ECS) down-regulates the induction of c-fos in response to an acute test seizure (Winston et al. 1990). Moreover, down-

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regulation of c-fos induction was determined to be different from the desensitization observed during the refractory period after a single, acute seizure (see Winston et al. 1990). These results indicate that induction of c-fos is influenced by prior exposure to seizure-induced neuronal stimulation.

The finding that chronic ECS treatment attenuates the induction of c-fos in response to an acute seizure raises the possibility that such chronic treatment may also alter the induction of this IEG transcription factor in response to other, more physiological stimuli. Thus, chronic ECS could result in down-regulation of c-fos induction in response to many different types of neuronal or behavioral stimuli. The first objective of this study is to test this hypothesis, by examining the influence of chronic ECS on the induction of c-fos mRNA in response to acute stress. Previous studies have demonstrated that acute restraint stress increases levels of c-fos mRNA in rat frontal cortex and other brain regions (Gubits et al. 1989; Bing et al. 1991), indicating that this stress paradigm would be appropriate for the present study.

Down-regulation of ECS-induced c-fos expression is observed after chronic, but not acute ECS treatment (Winston et al. 1990), a time course consistent with the treatment time required for the therapeutic, antidepressant action of ECS. This raises the possibility that down-regulation of c-fos induction is an action shared by other antidepressant treatments. The second objective of this study is to examine this possibility by studying the regulation of c-fos induction by antidepressant drug treatments. Several different classes of antidepressant drugs were examined, including a monoamine oxidase inhibitor (tranylcypromine), a nonselective monoamine re-uptake inhibitor (imipramine), a selective norepinephrine re-uptake inhibitor (desipramine), and a selective serotonin re-uptake inhibitor (sertraline).

The results of these studies demonstrate that chronic, but not acute, administration of ECS or antidepressant drugs down-regulates the induction of c-fos in response to acute restraint stress, supporting the hypothesis that regulation of c-fos expression is a common postreceptor site of action of antidepressant treatments.

MATERIALS AND METHODS

Animals and Treatment Paradigms

Male Sprague Dawley rats (150 to 200 g) (CAMM, Wayne, NJ) were group housed and maintained on a 12-hour light-dark cycle with food and water freely available. Animals were administered ECS via earclip electrodes (50 mA, 0.3 seconds) once daily for 1 to 9 days. Tranylcypromine (7.5 mg/kg for the first 7 days, and then 10 mg/kg for 14 days), imipramine (15 mg/kg), desipramine (15 mg/kg), and sertraline (10 mg/kg) were administered via intraperitoneal injection (IP) once daily for 1 to 21 days as indicated. Chronic cocaine (15 mg/kg, IP twice daily for 14 days) and haloperidol (1 mg/kg, IP once daily for 21 days were studied to determine the pharmacological specificity of the observed antidepressant effects. Sham treated animals were handled identically as those that received ECS, or received saline injections of the same volume as that given for drug treatments. In some experiments, one-half of the sham and one-half of the ECS- or drug-treated animals were also administered restraint stress (45 minutes) 18 hours after the last ECS or drug treatment. Animals were sacrificed either 18 hours after the last ECS or drug treatment or immediately after the 45 minute restraint stress challenge. Sections of frontal cortex were dissected from brain for RNA extraction as described below. All animal use procedures were in strict accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Yale Animal Care Committee.

RNA Analysis

Total RNA was isolated from sections of frontal cortex by the guanidine isothiocyanate/cesium chloride centrifugation method (see Winston et al. 1990 and Duman et al. 1992). Levels of c-fos, c-jun, and NGFI-A mRNA were determined by Northern blot analysis using random-primed, [^{32}P]-labeled cDNA probes as previously described (Duman et al. 1992). Briefly, 20 μg of total RNA was electrophoresed on a 1% agarose gel and the RNA was transferred to nitrocellulose filters. The resulting filters were then incubated with the [^{32}P]-labeled probes for 18 hours at 45°C and washed at high stringency. The radiolabeled mRNA bands were visualized by autoradiography and were quantitated by densitometry. Levels of total RNA for each lane were determined to be approximately equal by reprobing the nitrocellulose filters with a [^{32}P]-labeled cyclophilin cDNA probe.

RESULTS

Chronic ECS Treatment Down-Regulates Stress Induction of c-fos mRNA

To address the first objective of this study, the influence of chronic administration of ECS on the induction of c-fos mRNA in response to acute restraint stress was examined. Acute restraint stress (45 minutes) alone increased levels of c-fos mRNA five- to sixfold relative to resting levels in rat frontal cortex (Figures 1 and 2) as previously reported (Gubits et al. 1989; Bing et al. 1991). Chronic administration of ECS significantly decreased the induction of c-fos mRNA in response to acute re-

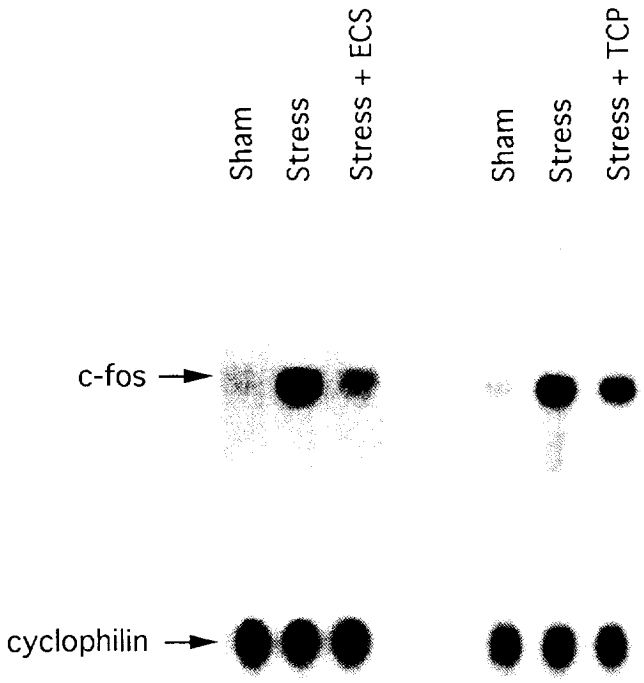

Figure 1. Chronic ECS or tranylcypromine treatments down-regulate stress-induced levels of c-fos mRNA in frontal cortex. Rats were administered ECS (9 days) or tranylcypromine (TCP, 21 days), and control animals received sham treatment. Eighteen hours after the last treatment rats were subjected to acute restraint stress (45 minutes) and levels of c-fos mRNA were determined by northern blot using a [^{32}P]-labeled c-fos cDNA probe as described in Materials and Methods. Shown are representative autoradiograms of c-fos mRNA, demonstrating that chronic ECS or TCP treatments decreased the induction of c-fos mRNA in response to acute restraint stress. To demonstrate that levels of RNA per lane were equivalent, the filters were reprobed with a [^{32}P]-labeled cyclophilin cDNA probe. Similar results were obtained in four to six separate determinations.

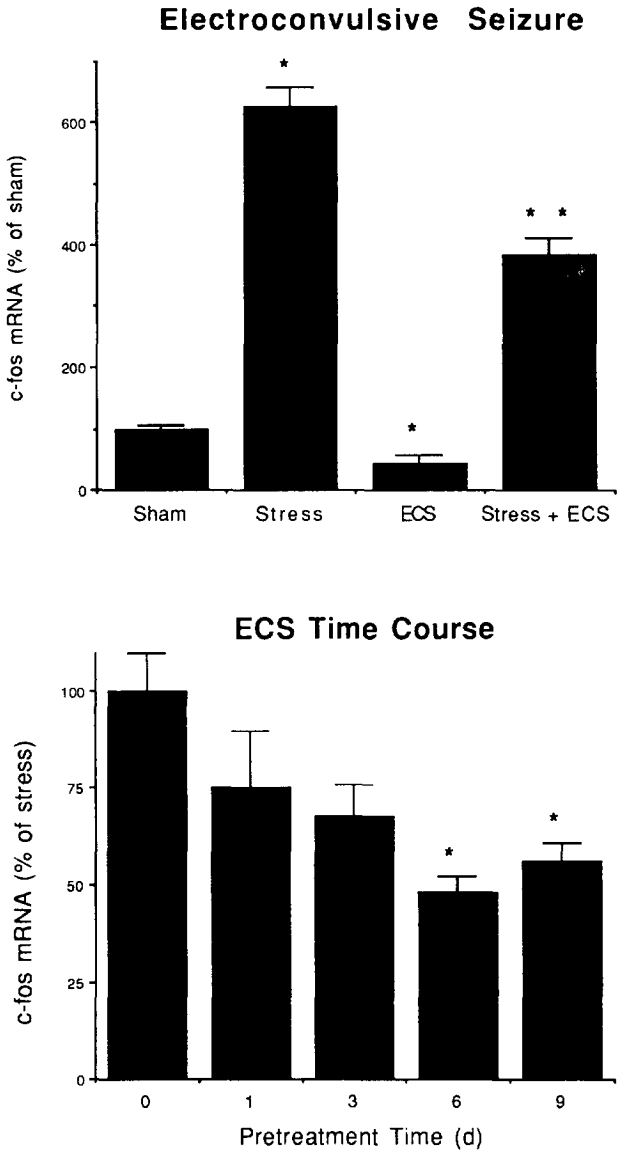

Figure 2. Chronic, but not acute, ECS treatment down-regulates stress-induced levels of c-fos mRNA. Rats were administered ECS for 9 days (upper panel) or 1 to 9 days (lower panel) and 18 hours after the last treatment were subjected to acute restraint stress (45 minutes) as described in Materials and Methods. The influence of chronic ECS (9 days) on resting (no stress) levels of c-fos mRNA was also determined 18 hours after the last treatment (upper panel). Levels of c-fos mRNA were determined by northern blot and resulting autoradiograms were quantitated by densitometric scanning. The amount of RNA in each sample was determined to be equivalent by reprobing nitrocellulose filters with [^{32}P]-labeled cyclophilin cDNA. In the upper panel, results are expressed as percent of sham and in the lower panel as percent of stress alone. Each bar is the mean ± SEM of three to five separate determinations. * $p < 0.05$ compared to sham; ** $p < 0.05$ compared to stress (one-way ANOVA and Fishers test).

straint stress by approximately 50% (Figures 1 and 2). Down-regulation of c-fos induction was dependent on chronic (6 or 9 days) ECS treatment, as short-term (1 or 3 days) treatment did not significantly influence c-fos induction (Figure 2). Chronic ECS treatment also decreased resting (no restraint stress) levels of c-fos mRNA in frontal cortex (Figure 2) as previously reported (Winston et al. 1990).

Chronic Tranylcypromine or Imipramine Treatments Down-Regulate Stress Induction of c-fos mRNA

To address the second objective of this study, the influence of other antidepressant treatments on the induction of c-fos mRNA in response to stress was examined. The first drugs to be examined were tranylcypromine and imipramine, which nonselectively increase

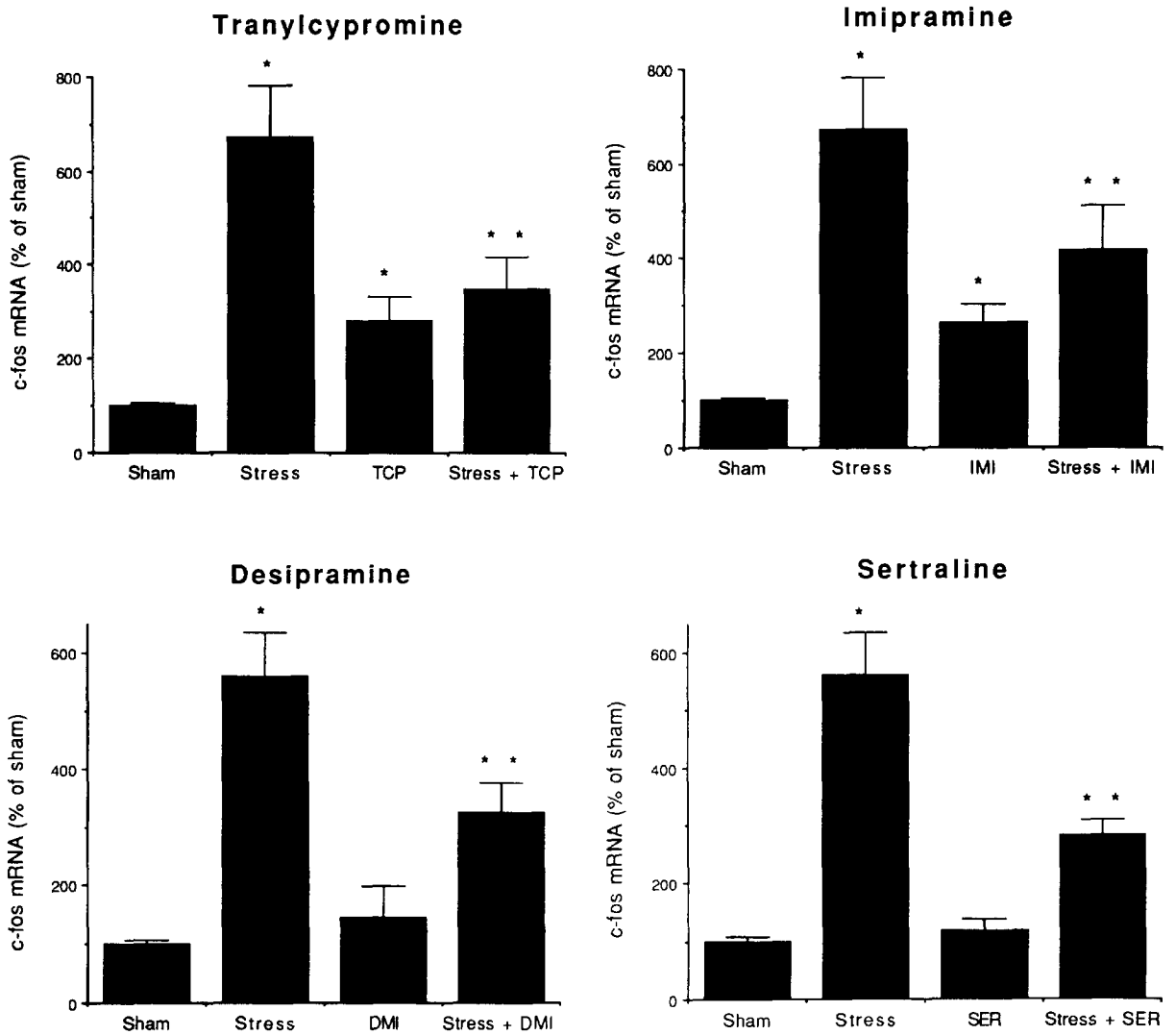

Figure 3. Chronic antidepressant drug treatments down-regulate stress-induced levels of c-fos mRNA. Rats were administered tranylcypromine (TCP), imipramine (IMI), desipramine (DMI), sertraline (SER), or vehicle (sham) for 21 days, and 18 hours after the last treatment the rats were subjected to acute restraint stress (45 minutes). The influence of chronic drug treatments on resting (no restraint stress) levels of c-fos mRNA was also determined 18 hours after the last treatment. Levels of c-fos mRNA were determined by northern blot and resulting autoradiograms were quantitated by densitometric scanning. The amount of RNA in each sample was determined to be equivalent by reprobing nitrocellulose filters with [^{32}P]-labeled cyclophilin cDNA. The results are expressed as percent of sham and are the mean ± SEM of three to five separate determinations. * $p < 0.05$ compared to sham; ** $p < 0.05$ compared to stress (one-way ANOVA and Fishers test).

levels of norepinephrine and serotonin. Chronic tranylcypromine treatment significantly decreased the induction of c-fos mRNA in response to acute restraint stress (Figures 1 and 3). Down regulation of c-fos induction was observed after chronic (21 days), but not acute (2 hours) or short-term (10 days), tranylcypromine treatment (Figure 4). Chronic administration of imipramine (21 days) also significantly decreased the induction of c-fos in response to acute restraint stress (Figure 3), whereas acute (2 hours) or short-term (7 days) imipramine treatment did not significantly influence stress-induced levels of c-fos (Figure 4). In contrast to ECS, resting levels of c-fos mRNA were significantly increased by chronic tranylcypromine or imipramine treatments, determined 18 hours after the last treatment (Figure 3).

Chronic Desipramine or Sertraline Treatments Down-Regulate Stress Induction of c-fos mRNA

The influence of desipramine and sertraline, two additional antidepressant drugs that selectively inhibit the

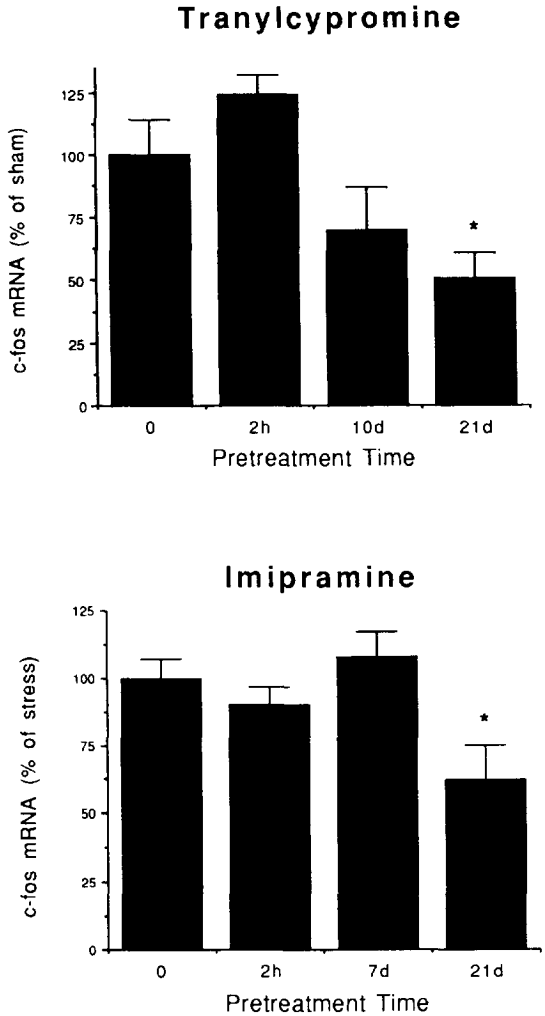

Figure 4. Time course for down-regulation of stress-induced levels of c-fos mRNA by tranylcypromine and imipramine treatments. Rats were administered tranylcypromine, imipramine, or vehicle (0) for the times indicated, and 18 hours after the last treatment were administered restraint stress for 45 minutes. Levels of c-fos mRNA were determined by northern blot as described in Materials and Methods, and resulting autoradiograms were quantitated by densitometric scanning. The results are presented as percent of stress and are the mean ± SEM of three to five separate determinations. * $p < 0.05$ compared to stress (one-way ANOVA and Fishers test).

re-uptake of norepinephrine and serotonin, respectively, on the induction of c-fos was also examined. Chronic (21 days) administration of either desipramine or sertraline also down-regulated the induction of c-fos in response to acute stress (Figure 3). This effect was also dependent on chronic treatment, as acute (1 day) desipramine and sertraline treatments did not significantly influence the induction of c-fos mRNA [107 ± 23 and 96 ± 6% of stress, respectively (mean ± SEM of four separate determinations)]. Chronic (21 days) administration of these selective reuptake inhibitors did not significantly influence resting levels of c-fos mRNA in frontal cortex (Figure 3).

Chronic Administration of Nonantidepressant Psychotropic Drugs Does Not Influence Stress Induction of c-fos mRNA

To determine the pharmacological specificity of this effect, the influence of two nonantidepressant psychotropic drugs, cocaine and haloperidol, on the induction of c-fos was examined. Cocaine is a nonantidepressant monoamine reuptake inhibitor, and haloperidol is an antipsychotic with D_2-dopamine receptor antagonist properties. Chronic administration of cocaine (14 days) or haloperidol (21 days), treatment regimens that have been used to study the chronic actions of these psychotropic drugs, did not significantly influence the induction of c-fos mRNA in response to acute stress [97 ± 8 and 97 ± 5% of stress, respectively (mean ± SEM of four separate determinations)].

Chronic Antidepressant Treatment Down-Regulates Stress Induction of NGFI-A mRNA

The influence of antidepressant treatment on the induction of two other immediate early gene transcription factors, c-jun and NGFI-A, was also examined. C-Jun dimerizes with c-Fos to form the AP-1 DNA binding complex, whereas NGFI-A recognizes a completely different DNA binding site (Morgan and Curran 1991). Levels of c-jun mRNA were not significantly influenced either by acute stress or by the chronic antidepressant treatments examined (Figure 5). However, chronic (21 days) administration of ECS or tranylcypromine significantly blocked the induction of NGFI-A by acute restraint stress in frontal cortex (Figure 5). Preliminary studies indicate that chronic imipramine treatment also decreases the induction of NGFI-A mRNA by acute restraint stress (not shown).

DISCUSSION

The results of this study demonstrate that chronic, but not acute, ECS treatment decreases the induction of c-fos mRNA in response to acute restraint stress, indicating that c-fos responsiveness to physiological stimuli is decreased by ECS treatment. Moreover, the results demonstrate that chronic, but not acute, administration of several other antidepressant drugs also down-regulates c-fos induction in response to acute restraint stress. These findings are in agreement with a recent, preliminary report that chronic imipramine treatment decreases the induction of c-fos in response to acute swim stress (Duncan et al. 1992). Taken together, the

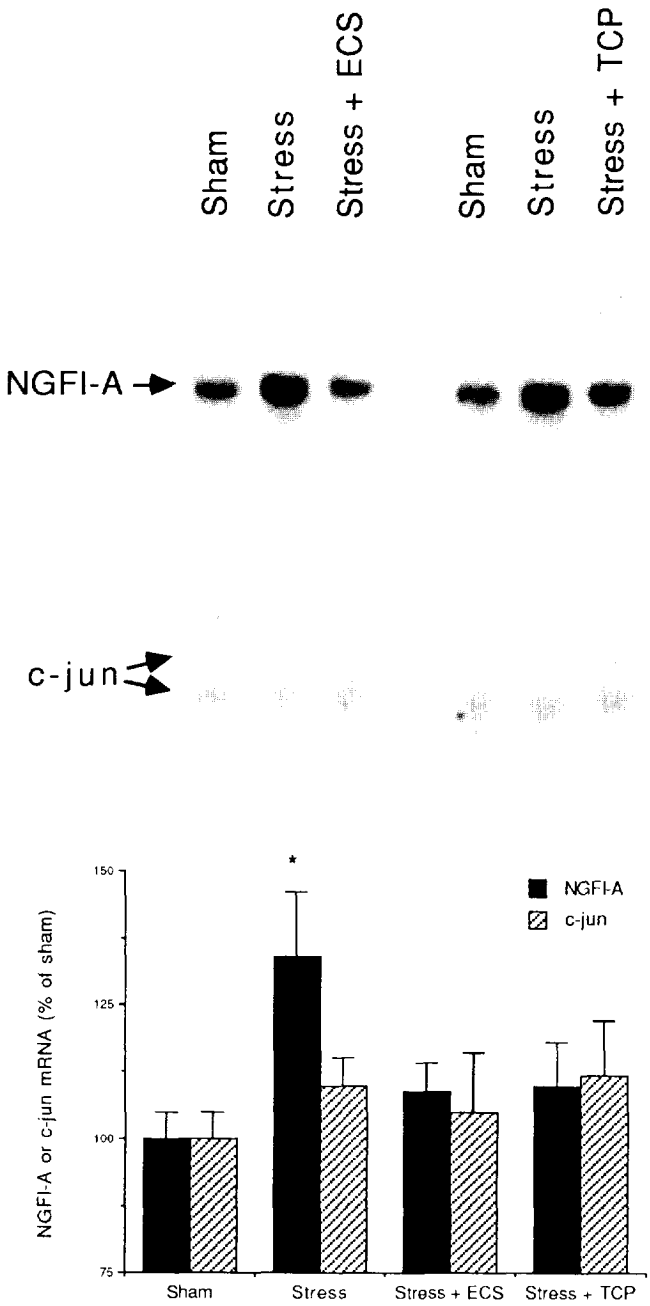

Figure 5. Chronic ECS or tranylcypromine treatments down-regulate stress-induced levels of NGFI-A mRNA. Rats were administered ECS (9 days) or tranylcypromine (TCP, 21 days) and 18 hours after the last treatment animals were subjected to acute restraint stress (45 minutes). Levels of NGFI-A or c-jun mRNA were determined by northern blot exactly as described in Materials and Methods. Shown are representative autoradiograms of NGFI-A and c-jun mRNA (upper panel), and quantitation of radiolabeled bands by densitometric scanning (lower panel). The results are presented as percent of sham and are the mean ± SEM of three to four separate determinations. * $p < 0.05$ compared to sham (one-way ANOVA and Fishers test).

results indicate that c-fos responsiveness to stressful stimuli can be attenuated by prior exposure to antidepressant treatments.

The mechanism(s) that underlie the down-regulation of c-fos induction by antidepressants could involve long-term adaptations of neuronal function in response to these chronic treatments. In this regard, many antidepressant treatments down-regulate the density and/or function of β-adrenergic receptors in frontal cortex (Sulser et al. 1978; Heninger and Charney 1987; Hosoda and Duman 1993). The induction of c-fos in response to restraint stress is mediated, in part, by activation of β-adrenergic receptors (Bing et al. 1991), and down-regulation of β-adrenergic receptors would be expected to reduce the ability of stress to induce c-fos expression. However, it is notable that the serotonin selective reuptake inhibitors are less effective in down-regulating β-adrenergic receptors, suggesting that adaptations of other receptor-coupled second messenger systems mediate the actions of these drugs (Heninger and Charney 1987). Chronic administration of serotonin selective reuptake inhibitors, as well as other types of antidepressants, results in adaptations of serotonin receptor subtypes (Heninger and Charney 1987), and it is possible that these effects are also involved in down-regulation of c-fos induction. For example, activation of 5-HT_2 receptors is reported to increase c-fos induction in cerebral cortex (Leslie et al. 1993), although the role of this and other 5-HT receptor subtypes in the c-fos response to stress has not been determined.

The ability of antidepressants to decrease c-fos induction could also be mediated by adaptations of post-receptor, intracellular sites. In this regard, expression of c-Fos protein is known to be involved in autoregulation of c-fos gene transcription. Acute seizure transiently increases the levels of c-fos mRNA and subsequently c-Fos protein; during the time when levels of c-Fos protein are elevated (but levels of c-fos mRNA have returned to control), induction of c-fos mRNA is desensitized (Morgan et al. 1987). Thus, desensitization of c-fos induction is temporally correlated with a transient elevation of c-Fos protein (Morgan et al. 1987), which could act in an "autoregulatory" manner to inhibit c-fos transcription as demonstrated in cultured cells (Sassone-Corsi et al. 1988). Preliminary studies demonstrate that chronic administration of tranylcypromine and imipramine increase levels of c-Fos protein (not shown), which could contribute to the down-regulation of c-fos induction via an autoregulatory mechanism. Although chronic ECS decreases levels of c-Fos protein (Winston et al. 1990; Hope et al. 1994), recent studies demonstrate that chronic ECS, as well as tranylcypromine, increase the expression of at least two "chronic" c-Fos related antigens (Fras) that may also influence the induction of c-fos (Hope et al. 1994). It is conceivable that desipramine and sertraline treat-

ments also influence levels of c-Fos or Fras, even though levels of c-fos mRNA were not significantly increased. The influence of these and other antidepressant treatments on the expression of c-Fos and chronic Fra proteins, as well as the exact role of these transcription factors in regulating c-fos gene transcription, remains to be determined.

In addition to these possibilities, other antidepressant-induced adaptations of postreceptor intracellular pathways could also influence c-fos expression. For example, chronic adaptations of second messenger-dependent protein kinases could influence the ability of stress to induce c-fos expression. In this regard, chronic antidepressant treatment has been reported to result in translocation of cAMP-dependent protein kinase to the nucleus (Nestler et al. 1989). In addition to activating certain transcription factors, such as CREB (cAMP response element binding protein), which stimulate gene transcription, translocation of cAMP-dependent protein kinase could result in activation of repressors, such as CREM (CRE modulator), which inhibit gene transcription (Foulkes et al. 1991; Molina et al. 1993).

The mechanisms underlying down-regulation of NGFI-A mRNA by chronic antidepressant treatments are not known, but could be similar to those discussed for induction of c-fos. Thus, the receptor-coupled second messenger systems that mediate the induction of NGFI-A mRNA (see Morgan and Curran 1991) could be down-regulated by chronic antidepressant treatment, or induction of NGFI-A may be influenced by expression of chronic Fras or other transcription factors. Alternatively, the protein product of NGFI-A could autoregulate its own transcription, although the influence of chronic antidepressant treatments on levels of NGFI-A protein has not been determined.

Regardless of the mechanisms, the results of this study indicate that down-regulation of c-fos induction in response to stress is a common action of antidepressant treatments. This possibility is supported by the finding that down-regulation of c-fos was dependent on chronic treatment, in agreement with the time required for the therapeutic action of antidepressant treatments (Heninger and Charney 1987). In this regard, c-fos induction was most rapidly down-regulated by ECS, which is considered the fastest-acting, as well as most effective, treatment for depression. This possibility is further supported by the finding that several different classes of antidepressants, including those treatments that selectively inhibit the reuptake of norepinephrine or serotonin, down-regulate c-fos induction. In contrast, chronic administration of two nonantidepressant psychotropic drugs, cocaine and haloperidol, did not influence the induction of c-fos. These findings suggest that down-regulation of c-fos induction is a postreceptor site of convergence for the action of antidepressant treatments and that this effect is pharmacologically specific to antidepressants. Such an effect is of particular interest because careful review of prior literature and recent studies of atypical antidepressants does not provide strong evidence that there is a common neurochemical action of antidepressants at the level of monoamine neurotransmitters or their receptors. Further studies will be needed to examine the influence of additional atypical antidepressants on the induction of c-fos to determine if this is an action common to all antidepressant treatments.

Although the target genes regulated by c-fos and NGFI-A remain largely unknown, it is conceivable that these transcription factors play a role in the regulation of other target proteins involved in long-term adaptive responses to antidepressant treatments. For example, recent studies have demonstrated that antidepressant treatments influence the expression of β_1-adrenergic receptors, 5-HT_2 receptors, novel transcription factors, and neurotrophins (Butler et al. 1993; Hosoda and Duman 1993; Morinobu and Duman 1993; Hope et al. 1994). In addition, down-regulation of c-fos induction could contribute to reversal or blockade of the actions of stress that are involved in precipitating or exacerbating periods of depression. Future studies will examine the role of c-fos and NGFI-A in these and other neurochemical adaptations to chronic antidepressant treatment, and will attempt to identify additional target genes regulated by these IEG transcription factors.

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REFERENCES

Bing G, Filer D, Miller JC, Stone EA (1991): Noradrenergic activation of immediate early genes in rat cerebral cortex. Mol Brain Res 11:43–46

Butler MO, Morinobu S, Duman RS (1993): Chronic electroconvulsive seizures increase the expression of serotonin 2 receptor mRNA in rat frontal cortex. J Neurochem 61:1270–1276

Curran T (1988): The Fos oncogene. In Reddy EP, Skalka AM, Curran T, (ed), The Hippocampus. New York, Elsevier, pp 307–325

Dragunow M, Robertson HA (1987): Kindling stimulation induces c-fos protein(s) in granule cells of the rat dentate gyrus. Nature 329:441–442

Duman RS, Craig JS, Winston SM, Deutch AY, Hernandez TD (1992): Amygdala kindling potentiates seizures-stimulated immediate-early gene expression in rat cerebral cortex. J Neurochem 59:1753–1760

Duncan GE, Johnson KB, Breese GR (1992): Imipramine an-

tagonizes neuroanatomically selective alterations of 2-DG and induction of Fos-like immunoreactivity induced by stress. Amer Col Neuropsychopharmac 32:85

Foulkes NS, Laoide BM, Schlotter F, Sassone-Corsi P (1991): Transcriptional antagonist cAMP-responsive element modulator (CREM) down-regulates c-fos cAMP-induced expression. Proc Natl Acad Sci USA 88:5448–5452

Gubits RM, Smith TM, Fairhurst JL, Yu H (1989): Adrenergic receptors mediate changes in c-fos mRNA levels in brain. Mol Brain Res 6:39–45

Heninger GR, Charney DS (1987): Mechanism of action of antidepressant treatments: Implications for the etiology and treatment of depressive disorders. In Meltzer H, (ed), Psychopharmacology. New York, Raven Press, pp 535–544

Hope BT, Kelz MB, Duman RS, Nestler EJ (1994): Chronic electroconvulsive seizure (ECS) treatment results in expression of a long-lasting AP-1 complex in brain with altered composition and characteristics. J Neurosci 14: 4318–4328

Hosoda K, Duman RS (1993): Regulation of β_1-adrenergic receptor mRNA and ligand binding by antidepressant treatments and norepinephrine depletion in rat frontal cortex. J Neurochem 60:1335–1343

Leslie RA, Moorman JM, Coulson A, Grahame-Smith DG (1993): Serotonin 2/1C receptor activation causes a localized expression of the immediate-early gene c-fos in rat brain: Evidence for involvement of dorsal raphe nucleus projection fibres. Neurosci 53:457–463

Molina CA, Foulkes NS, Lalli E, Sassone-Corsi P (1993): Inducibility and negative autoregulation of CREM: An alternative promoter directs the expression of ICER, an early response repressor. Cell 75:875–886

Morgan JI, Curran T (1991): Stimulus-transcription coupling in the nervous system: involvement of the inducible proto-oncogenes for and jun. Annu Rev Neurosci 14: 421–451

Morgan JI, Cohen DR, Hempstead JL, Curran T (1987): Mapping patterns of c-fos expression in the central nervous system after seizure. Science 237:192–197

Morinobu S, Duman RS (1993): Induction of BDNF mRNA by electroconvulsive seizure (ECS) and antidepressants in rat frontal cortex. Soc Neurosci Abst 19:499

Nestler EJ, Terwilliger RZ, Duman RS (1989): Chronic antidepressant administration alters the subcellular distribution of cyclic AMP-dependent protein kinase in rat frontal cortex. J Neurochem 53:1644–1647

Sagar SM, Sharp FR, Curran T (1988): Expression of c-fos protein in brain: Metabolic mapping at the cellular level. Science 240:1328–1331

Sassone-Corsi P, Sisson JC, Verma IM (1988): Transcriptional autoregulation of the proto-oncogene fos. Nature 334: 314–319

Sulser F, Vetulani J, Mobley PL (1978): Mode of action of antidepressant drugs. Biochem Pharmacol 27:257–261

Winston SM, Hayward MD, Nestler EJ, Duman RS (1990): Chronic electroconvulsive seizures down-regulate expression of the immediate-early genes c-fos and c-jun in rat cerebral cortex. J Neurochem 54:1920–1925